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Breast Cancer (WJ Gradishar, Section Editor)

Understanding the Clinical Implications of Low Penetrant Genes and Breast Cancer Risk

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Opinion statement

Since the 2013 Supreme Court declaration, panel testing for hereditary cancer syndromes has evolved into the gold standard for oncology germline genetic testing. With the advent of next-generation sequencing, competitive pricing, and developing therapeutic options, panel testing is now well integrated into breast cancer management and surveillance. Although many established syndromes have well-defined cancer risks and management strategies, several breast cancer genes are currently classified as limited-evidence genes by the National Comprehensive Cancer Network (NCCN). Follow-up for individuals with mutations in these genes is a point of contention due to conflicting information in the literature. The most recent NCCN guidelines have stratified management based on gene-specific cancer risks indicating that expanding data will allow for better recommendations as research progresses. The evolving management for these genes emphasizes the clinicians' need for evidence-based understanding of low penetrance breast cancer genes and their implications for patient care. This article reviews current literature for limited evidence genes, detailing cancer risks, association with triple-negative breast cancer, and recommendations for surveillance. A brief review of the challenges and future directions is outlined to discuss the evolving nature of cancer genetics and the exciting opportunities that can impact management.

Introduction

Genetic testing for hereditary breast cancer syndromes has evolved since 2013, mirroring the tremendous growth in technology available for testing [1]. Multiple commercial laboratories in the USA offer increasingly competitive cancer genetic testing, custom panel selections, RNA analysis, and paired germline/somatic testing [1–3]. Keeping with this changing technology, the National Comprehensive Cancer Network (NCCN) version 2.2021 discusses the evidence for increased risk of breast cancer based on current literature. It offers management recommendations by categorizing the strength of supportive evidence for these genes as "very strong," "strong," "limited," and "insufficient/no evidence" [4]. Genes that fall in the "very strong" category are the two well-established classic hereditary breast and ovarian cancer genes—BRCA1 and BRCA2. The BRCA1 and BRCA2 genes are associated with high penetrance for breast cancer, with absolute risk estimates greater than 60%. Genes that fall in the "strong" category include high and moderate penetrance genes linked to other established hereditary cancer syndromes. The ATM, CDH1, CHEK2, NF1, PALB2, PTEN, STK11, and TP53 genes fall in this category. The breast cancer risk estimates for these genes fall between 15 and 60%, with moderate penetrance genes at the lower end of that spectrum and high penetrance genes at the upper end.

Mutations in genes defined as "limited evidence" display low penetrance for breast cancer with evidence based on small sample sizes or case series. The BARD1, BRIP1, MLH1, MSH2, MSH6, PMS2, NBN, RAD51C, and RAD51D genes fall within this category. Their association with breast cancer continues to be a subject of debate, with risk estimates stated as undefined. The NCCN guidelines for these categories offer follow-up and management options for each gene uniquely crafted based on supportive literature [4].

Due to the increasingly competitive cost of panel genetic testing, there has been a growth in the uptake of genetic testing. This growth has translated into improved data available for research resulting in a better characterization of the cancer risks, management options, and follow-up for mutation carriers. This review will outline and summarize the current state of knowledge using the most recent and relevant literature for these limited evidence genes. Since genetic testing can yield several types of results, in keeping with the American College of Medical Genetics (ACMG) classification, we will consider all cancer risks to be linked to likely pathogenic and pathogenic variants in described genes [5].

Methods

A literature review was performed to capture relevant and recent publications. A systematic analysis was performed by pairing search terms "breast cancer" and "management" individually with the genes BARD1, BRIP1, MLH1, MSH2, MSH6, PMS2, NBN, RAD51C, and RAD51D. The review was performed in PubMed with combinations for individual genes to obtain maximum results. The results were then stratified by "most relevant" and "recent" to include all relevant studies. The search was performed on 02/23/2021 with no additional limits. The search was complemented by consulting references listed in the NCCN guidelines and review articles. Finally, all publications of utility cascading from the review of this body of work were included.

The exclusion criteria entailed case reports, non-English papers, and animal studies. No metrics or meta-analysis was performed in this study. From this search, a total of 79 papers were obtained. All 79 abstracts were evaluated to check for relevance. A total of 52 articles were used in the construction of this review. The common reasons for exclusion included irrelevance to the genes under evaluation, systemic therapy-related works, and articles related to tumor analysis.

BARD1

The BRCA1 Associated Ring Domain 1 (BARD1) gene is a binding partner to the BRCA1 gene. The BARD1 gene protein has tumor suppressor functions, and mutations affecting splice sites in this gene have been shown to cause oncogenic functions [6].

Association with breast cancer

In 2015, Tung et al. published a study that reported mutations in the BARD1 gene to have no conclusive evidence for breast cancer risks [7]. In 2017, Kurien et al. outlined an association of BARD1 to breast cancer with a relative risk of 1.94 [8]. Between 2017 and 2021, several studies have described BARD1 as a low- or moderate-penetrance breast cancer gene with an odds ratio (OR) ranging from 2.16 to 2.33 [9–11]. The association of BARD1 mutations with triple-negative breast cancer (TNBC) has also been described with the OR ranging between 5.92 and 9.76 [12, 13].

Lifetime cancer risk estimates

BARD1 gene mutations have a lifetime breast cancer risk of at least 20%, with risk estimates ranging between 17 and 30% [11, 14]. The association between TNBC and BARD1 gene mutations has been reported in multiple publications [12, 15]. This association in individuals of African American ancestry has been linked with a high to moderate risk for breast cancer [13••]. The absolute breast cancer risk estimate for BARD1 mutation carriers in individuals up to age 85 was 21% among Caucasians and 39% in African Americans [13••].

Management and therapy

In 2015, Tung et al. discussed that women with mutations in the BARD1 gene should undergo screening based on a family history model. Since then, multiple studies demonstrate the importance of enhanced screening in individuals with BARD1 gene mutations [6, 7, 11, 13, 14].
The NCCN guidelines version 2.2021 recognized BARD1 as a gene with limited evidence for increased breast cancer risk and strong evidence for association with TNBC. Per NCCN, management recommendations for BARD1 currently include screening with an annual mammogram and considering breast MRI starting at age 40 [4]. Additionally, treatments that utilize antibodies to detect BARD1 isoforms have been proposed as a possible breast cancer screening tool [6].

BRIP1

BRCA1 Interacting Protein 1 (BRIP1) gene encodes a protein that binds with BRCA1 and is part of the DNA repair mechanism via homologous recombination. BRIP1 is one of the Fanconi Anemia (FA) genes with biallelic mutations causing FANC group J [16–18].

Association with breast cancer

Studies published before 2010 have suggested that mutations in the BRIP1 gene could be associated with a modestly increased risk for breast cancer, especially in individuals with early-onset breast cancer or a family history of breast cancer [19, 20]. Additional reports between 2017 and 2019 stated that BRIP1 has an increased risk for breast cancer with an OR between 1.5 and 1.63 [9, 10]. Hu et al.'s study did not show any association of increased risk for breast cancer with mutations in the BRIP1 gene [15•]. Other studies have discussed the association of BRIP1 mutations with a statistically significant and clinically relevant risk for TNBC with an OR greater than 2 [13, 14].

Lifetime cancer risk estimates

It is well established that mutations in the BRIP1 gene confer a moderately increased risk for ovarian cancer [4, 8, 9, 18]. Multiple studies have shared from their research that there is limited evidence of any association between breast cancer and BRIP1 mutations, particularly truncating mutations [1, 8, 17, 18].

Management and therapy

Several sources recommend risk-reducing salpingo-oophorectomy (RRSO) for the ovarian cancer risk conferred by mutations in the BRIP1 gene and the NCCN guidelines version 2.2021 encourage discussing this between ages 45 and 50 [4, 8, 18]. The NCCN guidelines state that there is evidence for breast cancer risk to be potentially increased in females with a BRIP1 mutation. Due to the absence of conclusive data to support this risk screening, the current recommendation is to manage individuals based on their family history [4].

NBN

The NBN gene encodes for the protein Nibrin which forms an integral component of the MRN complex which is involved in the repair of double-stranded breaks and the maintenance of chromosomal integrity. Biallelic mutations in the NBN gene result in a rare autosomal recessive syndrome called Nijmegen breakage syndrome [16, 21].

Association with breast cancer

In 2013, Zhang et al. published a study discussing the NBN c.657del5 mutation observed in the Slavic population and reported its association with breast cancer. Zhang et al.'s study was described by Easton et al. in 2015, discussing this variant's association with breast cancer. They outlined a relative risk of 2.7 and an absolute risk of 23% by age 80. Easton et al. discussed in their study that this association might be too imprecise to categorize with the limited data [1, 21].

Lifetime cancer risk estimates

In 2016, Tung et al. discussed the cumulative lifetime risk for cancer for mutations in the NBN gene to be greater than 20% [7]. All other studies evaluated in this review discussed the absence of statistically significant associations of NBN gene mutations with a risk for breast cancer [8–10, 14, 15, 22]. In 2018, Shemelis et al. discussed that variants in the NBN gene did not display any clinically relevant risk for TNBC [13••].

Management and therapy

According to NCCN 2.2021, there is insufficient data to determine NBN gene–specific breast cancer risks, so no management recommendations are currently available [4].

RAD51C and RAD51D

RAD51C and RAD51D genes are two of the five paralogs of RAD51 and work with other DNA repair genes on double-stranded breaks by homologous recombination. Biallelic mutations in the RAD51C gene are known to cause Fanconi Anemia Type O [16, 23].

Association with breast cancer

Several studies have shown that the RAD51C gene does not confer an increased risk for breast cancer [1, 7–10]. Since 2019, studies have reported an increased risk for breast cancer with mutations in the RAD51C gene [11, 23, 24]. In a study of the association between loss of function RAD51C mutations and breast cancers, the data yielded an OR of 8.67 [23]. Another study showed a more modest association with an OR of 1.93 [11••]. In 2020, Yang et al. discussed in their family-based study that the estimated relative risk for breast cancer for an individual with a mutation in the RAD51C gene is 1.99 [24].

In 2017, Kurien et al. reported that their study did not find an increased risk for breast cancer in those with mutations in the RAD51D gene [8]. Between 2017 and 2020, several studies reported RAD51D mutations as associated with a moderately increased risk for breast cancer, outlining an OR ranging between 1.80 and 3.07 [10, 11]. Yang et al. stated that the estimated relative risk for breast cancer in an individual with a RAD51D gene mutation is 1.83 [24]. In 2018, Shimelis et al. discussed that RAD51D was associated with a higher OR of 6.97 for TNBC [13••].

Lifetime cancer risk estimates

The association between mutations in the RAD51C and RAD51D gene with ovarian cancer is well established [1, 7, 9, 25].

In 2015, Easton et al. reported a limited association between RAD51D gene mutations and an increased risk of breast cancer [1]. Between 2020 and 2021, a few studies have described the overall lifetime risk for breast cancer between 20 and 46% for individuals with mutations in the RAD51C gene, calling it a moderate risk breast cancer gene [11, 14, 15, 24]. Since then, there has been a deluge of data supporting RAD51D's association with

breast cancer [10, 11, 13, 14, 24]. The absolute lifetime risk has been estimated to be between 20 and 46% based on data from these studies [11, 13, 14, 24].

In 2020, Yang et al. discussed that the estimated lifetime risk for breast cancer in their study was 21% till the age 80 for individuals with mutations in RAD51C or RAD51D gene. They suggested that the cancer risks could be as high as 44–46% for carriers with two or more first-degree relatives with breast cancer [24].

Two studies have discussed that RAD51C gene mutations were associated with a moderate risk for TNBC with OR >2 [13, 14]. RAD51C gene mutations are associated with a statistically significant high risk for TNBC in the African American population; while conferring a moderate risk of TNBC for the Caucasian population. Replication studies are needed to confirm this data and to promote appropriate clinical care [13••]. Tumor sequencing of germline RAD51C mutation carriers who have a diagnosis of breast cancer has found that biallelic inactivation of the RAD51C gene is associated with high HRD scores [23].

Since 2018, there have been reports discussing the association of RAD51D mutations with an increased risk for TNBC [13, 14]. In a unique study, Ma et al. reported the frequency of mutations in the RAD51D gene found in the Chinese population, specifically in individuals with TNBC. They stated an approximately tenfold increase in the risk for TNBC in the Chinese population than was reported in a western cohort. A single mutation—K91fs—was suggested as a founder mutation in the East Asian cohort. RAD51D variants can impact homologous recombination in TNBC cell lines, with further analysis suggesting vulnerability to PARP inhibitors [26].

Management and therapy

Multiple studies have supported RRSO to prevent ovarian cancer risks in individuals with RAD51C and RAD51D mutations, including NCCN, which recommends surgery at age 45 to 50 [4, 7, 8]. NCCN guidelines state limited evidence for increased breast cancer risk for individuals with RAD51C and RAD51D mutations with an absolute breast cancer risk outlined as 15–40%. Although this risk is equivalent to the risk for ATM mutations quoted by NCCN, no recommendations for breast surveillance are currently offered by NCCN for RAD51C or RAD51D mutation carriers [4, 24].

Hu et al. stated that enhanced breast cancer screening might be considered for carriers of mutations in the RAD51C gene based on their study [14]. A few studies have suggested considering additional breast cancer screening for individuals with RAD51D mutation, although no specific recommendations have been offered [13, 14].

Lynch syndrome

Lynch syndrome is an autosomal dominant cancer predisposition syndrome caused by germline mutations in one of five mismatch repair (MMR) genes—MLH1, MSH2, MSH6, PMS2, and EPCAM [27]. Substantial evidence is available for the association of Lynch syndrome with multiple cancers,

including colorectal, uterine, and ovarian cancer [28].

Several studies have discussed MMR gene mutations causing an increased risk for breast cancer and warranting additional breast screening. Data showed the mean age of breast cancer diagnosis as 52 in MMR mutation carriers with cancer risk till age 40 estimated to be 14.4% [29, 30]. This evidence is conflicting as other studies discussed no significant deviation from general population risks for individuals with MMR gene mutations [15, 31]. Win et al. proposed the need for large prospective cohort studies to better outline breast cancer risks for MMR gene mutation carriers [32].

Association with breast cancer

In 2015, Harkness et al. described the cumulative lifetime risk for breast cancer in MLH1 mutation carriers as 18.6%. Their study was based in the UK, with general population risk estimated as 7.5–8%, indicating more than twice the general population risk for breast cancer. Based on this estimate, their study discussed offering annual mammograms starting at age 40 [27]. Multiple other studies between 2015 and 2021 have found no significant associations between MLH1 mutations and an increased risk for breast cancer [8–10, 15, 31, 33].

For individuals with mutations in the MSH2 gene, several studies outline no increased risk for breast cancer [10, 27, 33]. A few studies discuss MLH2 as a low-risk breast cancer risk variant. Suszynska et al.'s study states a slightly increased risk for breast cancer for MSH2 mutation carriers with an OR of 1.5 [9•]. In a Canadian study, the breast cancer risk for MSH2 mutation carriers was three times the general population risk, with the lifetime risk quoted as 22% [34].

Of the Lynch syndrome genes, the most evidence is available for an association of MSH6 mutations with a low to moderate risk for breast cancer [9, 10]. Roberts et al. discussed that mutations in the MSH6 gene yield a cumulative breast cancer risk of 31.1% by age 60 [33]. Lu et al. also discussed a greater number of pathogenic variants in the MSH6 gene associated with an increased risk for breast cancer, stating an OR of 2.59 [35•]. One study reported no association with an increased breast cancer risk for MSH6 mutation carriers [8]. Multiple studies indicate that pathogenic variants in the MSH6 gene can be associated with a significantly increased risk for TNBC [13, 14]. Yi et al.'s study in the Chinese population discussed the relatively high prevalence of MSH6 mutations in individuals with triple-negative breast cancer reporting that the prevalence of MSH6 mutations was 7.6 [36].

Studies provide conflicting data for the association of PMS2 gene mutations with breast cancer. Supporting evidence indicates PMS2 mutations associated with an increased risk for breast cancer discussing a standardized incidence ratio between 2.9 and 3.8 [33, 37]. In 2018, Roberts et al. outlined a cumulative breast cancer risk of 37.7% by age 60 for PMS2 mutation carriers [33]. Other studies between 2017 and 2019 discussed no association of PMS2 mutations with increased breast cancer risks based on their data [8–10].

NCCN guidelines version 1.2020 for colorectal cancer syndromes discuss risk numbers and management options for colorectal, endometrial, ovarian, and other Lynch syndrome–associated cancers [28].

The NCCN guidelines version 2.2021 for breast and GYN cancer syndromes states limited breast cancer risk estimates for mutations in Lynch syndrome genes and does not offer any management recommendations [4]. Ten Broeke et al. and Roberts et al. suggested considering breast screening for individuals with PMS2 mutations, especially for individuals in families displaying a clustering of breast cancer [33, 37]. The above data also discussed MSH6 as a low-penetrance breast cancer gene. Additional research is required to estimate better the contributions of MSH6 and PMS2 to breast cancer risks.

Germline mutations in Lynch syndrome genes have yielded opportunities to consider immunotherapies as a management option in several different cancer types. Currently, deficient MMR or MSI-high status rarely appears in breast cancer. In 2018, Mills et al. discussed that MMR expression is unlikely to show utility as a screen for immunotherapy vulnerability in the breast tumor type [38].

Perspectives on surveillance

The NCCN breast and GYN guidelines version 2.2021 uses absolute breast cancer risk estimates to help direct screening for individuals with germline mutations. The lifetime risk estimates for breast cancer are formed using the average relative risk of cancer till age 70 or 80. For the low penetrance genes, NCCN guidelines recommend management based on family history at this time [4]. There is evidence supporting the role of family history as a critical driver in determining breast cancer risk in individuals with germline mutations [24]. Utilizing cancer risk models based on family history, such as Claus, BOADICEA, and Tyrer Cuzick, can help determine the role of increased screening in unaffected individuals.

Many factors can influence an individual's risk for breast cancer. Literature is available supporting different cancer risks based on the type of mutations in the same gene. There is also data to show that cancer risks for mutations in a gene can vary based on an individual's ancestry [26]. Therefore, it is necessary to utilize a multi-pronged approach when discussing management options with low-penetrance gene mutation carriers.

Recent literature has discussed the utility of using absolute risk estimates when offering screening recommendations for individuals with germline mutations. In 2016, Tung et al. discussed the advantages of using a 5-year relative risk model based on the SEER data to recommend screening for individuals with moderate-penetrance gene mutations. This study sets the benchmark in managing individuals with mutations in the moderate-risk breast cancer genes. Their logic outlined discussion of mammograms with individuals whose 5-year risk exceeded 1% regardless of their current age. They also proposed MRIs for individuals with a 5-year risk exceeding 2.2% (the highest 5-year breast cancer risk experienced by women in the general population). In 2020, McInnis et al. published data outlining the 5-year and lifetime risk estimates for unaffected women in the general population based on risk models. Their prospective 10-

year follow-up study determined that the 5-year measure performed as a better tool to estimate the breast cancer risk for individuals between age 20 and 39. The risk estimates for individuals 40 years and above were similar in both the 5-year and lifetime measure. They suggested that risk stratification using models that predict 5-year risks may be more accurate than lifetime risk estimates for unaffected women [39••]. Future studies quantifying relative risk based on age for low-penetrance genes can provide data to guide screening for this population [7].

Challenges

The limited information applicable to clinical management for individuals with mutations in low-penetrance genes poses a unique challenge for clinicians [40]. Although management based on family history is still recommended for these genes, the limited clinical utility often creates a frustrating experience for patients.

Guidelines help clinicians practice based on the consensus of professional societies. However, when societal recommendations differ, it can confuse healthcare providers working to promote genetic testing. In 2019, the American Society of Breast Surgeons released recommendations for physicians to offer genetic testing to all individuals diagnosed with breast cancer [41]. Since most insurance companies continue to use NCCN guidelines as a base to cover genetic testing, this can cause an undue financial burden on patients if their insurance does not deem the test medically necessary.

Even with genetic testing offered for all individuals who meet national guidelines for testing, genetic testing uptake is often unimpressive. A study of individuals diagnosed with ovarian cancer showed that only 30% of those who meet guidelines received testing between 2013 and 2014 [42]. Additional research is required to estimate genetic testing uptake in individuals who meet current national breast cancer genetic testing guidelines.

Discussion

The framework for interpreting low-penetrance breast cancer genes requires a multimodal approach involving the gene mutation, family history, and individual risk factors. Advances in technology in both the analysis and interpretive phases of genetic testing can promote testing's clinical validity [43, 44].

The polygenic risk score (PRS) is a tool to analyze multiple variants, each with a minor influence on cancer risks, to provide an overall risk stratification that is sufficient to improve screening efficacy. In 2017, Michailidou, K. et al. published data discussing GWAS-related PRS stratification, suggesting the use of PRS in risk models to improve genetic breast cancer risk estimates and direct screening strategies [45]. Increasing evidence suggests a highly polygenic architecture for genetic predisposition to breast cancer that will require further research [40]. A significant limitation of the PRS score is that the breast cancer risk stratification is currently only available to women of European ancestry. This limitation increases disparities in access to care for the minority population. The PRS is already being used to aid in screening decisions for women of European ancestry with uninformative genetic testing. At this time, NCCN does not offer any guidance in the utility of the PRS as a risk model to determine eligibility for increased breast surveillance [46••].

The debate on the utility of national genetic testing guidelines continues, with recent studies skewing this conversation. Yang et al. and Beitsch et al. concurrently published data in 2018 suggesting no improved mutation detection rate between individuals who did and did not meet national genetic testing guidelines. Both studies recommend all individuals with a personal or family history of cancer consider genetic testing [47, 48]. Other studies have suggested focusing efforts on detecting high-risk familial cancer syndromes using population screening. They opined that resources might be better utilized testing high-risk syndromes to reduce overall cancer risks and promote better care since the limited interpretation available for low-penetrance gene mutations limits their utility [40].

The use of precision medicine in cancer genetics has taken an enormous leap with the advent of PARP therapy which utilizes the concept of synthetic lethality. Tumors with BRCA mutations are exploited by inducing chemical inhibition using PARP inhibitors and promoting tumor cell death. The possibility of expanding PARP therapy to tumors with defects in other genes involved in the homologous recombination repair pathway is actively under research [16, 49]. Data presented at ASCO in 2020 by Tung et al. confirmed response to PARP in individuals with metastatic breast cancer, and germline PALB2 mutation carriers or somatic BRCA1/2 mutations. The study did not observe any response in individuals with ATM or CHEK2 mutations [50••]. Additional research under investigation includes understanding the use of kinases linked to synthetic lethality in the ATM/ATR pathways and new drugs relying on the nucleotide excision repair pathway to offer new avenues of therapy for individuals with breast cancer [51, 52].

Although constant improvement in cancer detection and cancer treatment is essential, screening is also a vital part of cancer prevention. A study from Poland explored the testing for BARD1 isoforms as a screening tool to determine risk status and monitor disease progression. Their research also discussed the potential of radiogenomics with BARD1 antibodies as an imaging biomarker to increase cancer cells' visibility [6]. Another study from China outlined the predictive value of DNA repair genes in breast cancer's postoperative metastasis. They described an immunohistochemical scoring mechanism that could predict an increased risk for metastasis [24]. Additional studies discuss combining double-stranded DNA repair inhibitors and other anti-cancer therapies as promising avenues for future drug exploration [53].

Conclusion

It is essential to consider family history as a critical driver in helping clinicians direct care for individuals with mutations in the low-penetrance breast cancer genes. In the presence of a strong family history of breast cancer, or higher risk model estimates, appropriate screening strategies will help capture cancer risk. The use of genetic information in medicine and clinical care continues to improve with leaps and bounds every decade. Promoting research, reporting on unique cases, and encouraging discussions on the screening recommendations for carriers of mutations in these genes will bring about meaningful conversations that direct care.

Declarations

Conflict of interest

Anusha Vaidyanathan is the Professional Issues Chair for the Texas Society of Genetic Counselors and the Research Chair for the National Society of Genetic Counselors (Cancer SIG). Both are unpaid positions.

Virginia Kaklamani has received speaker's honoraria and compensation for service as a consultant from Immunomedics, AstraZeneca, Daiichi Sankyo, Seattle Genetics, Puma Biotechnology, Pfizer, and Novartis, and has served on advisory boards for Puma Biotechnology, Radius Health, and Sanofi.

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